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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,074	04/19/2005	John Arthur Hohneker	ON/4-32515A	8731

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
07/20/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,074	HOHNEKER ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,41 and 43-45* is/are pending in the application.

4a) Of the above claim(s) *43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,41,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/03/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The amendment filed on 6/03/2010 in response to the Non-Final Office Action (03/01/2010) is acknowledged and has been entered.

Claims 32, 41 and 43-45 are currently pending.

Claim 43 is withdrawn from consideration as being drawn to a non-elected invention

Claims 32, 41 and 44-45 are currently under consideration.

Information Disclosure Statement

The information disclosure statement filed 6/03/2010 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. In the instant case, the Examiner acknowledges and appreciates Applicants submission of WO 99/43653 which is stated on the IDS to correspond to JP 2002504540. However, the Examiner recognizes that the actual JP document has not been submitted. All other references submitted have been considered and initialed.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32, 41 and 44-45 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Vite et al. (WO 99/02514, of record) in view of Nakajima et al. (Experimental Cell Research 1998; 241: 126-133).

Vite et al. teach a combination which comprises (a) a known anti-cancer agent or cytotoxic agent as a second drug and (b) a epothilone derivative which appears to encompass the claimed epothilone derivaties of formula I, wherein the second drug acts in a different phase of the cell cycle (page 2, Compound V and page 10, lines 22-29). Moreover, the WO document teaches that the compounds can be formulated with a pharmaceutical vehicle or diluent (page 11, lines 4-6). Lastly, the WO document teaches that epothilones A and B have been found to exert microtubule-stabilizing effects similar to paclitaxel and hence cytotoxic activity against rapidly proliferating cells, such as, tumor cells or other hyperproliferative cellular disease (page 1, lines 9-20).

Vite et al. do not explicitly teach that the second drug is a histone deacetylase inhibitor.

Nakajima et al. teach that a compound referred to as FR901228 is a histone deacetylase inhibitor which is remarkably active in vivo against experimental tumors and is currently under clinical investigation (abstract and page 132, 1st column, last paragraph). Moreover, Nakajima et al. teach that FR901228 exerts its effects by blocking cell cycle transition at G1 and G2/M phases (page 129, 1st column, 1st full paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the epothilone derivative as taught by Vite et al. with a histone deacetylase inhibitor as taught by Nakajima et al. One would have been motivated to do so because each have been individually taught in the prior art to be affecting at treating cancer. Hence, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, one of ordinary skill in the art would have reasonably expected to treat cancer since both had been demonstrated in the prior art to be effective.

Moreover, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the epothilone derivatives as taught by Vite et al. for

epothilone B in view of the teachings of Vite et al. One would have been motivated to do so because each of the agents have been taught in the prior art to be effective at inhibiting tumors cells.

In response to this rejection, Applicants contend that this rejection is based on the disclosure in Vite et al. which suggests that a benefit may be derived by combining the disclosed epothilones, which act at the G2/M phase of the cell cycle with another cytotoxic drug which acts at a different phase of the cell cycle. Thus, Applicants assert that that Vite et al. sets forth a hypothesis which at best demonstrates what one of ordinary skill in the art would consider obvious to try. However, Applicants contend that there is no data or other information which would lead the skilled artisan to understand this disclosure to be any more than a suggestion of a promising field for further research. Moreover, Applicants contend that it is clear that what is obvious to the Examiner was merely to explore the general approach of combining epothilones with compounds that target a different phase of the cell cycle. As such, Applicants assert that the rejection is improper based on the legal standards set forth in MPEP 2143(E) and the Federal Circuit's opinion in Bayer Schering Pharma AG vs. Parr Labratories, 575 F.3d 1341; 2009 U.S. App. LEXIS 17372; 91 U.S.P.Q.2.D 1569 (Fed. Cir. 2009), and the case law cited therein, both of which provides guidance about the application of an "obvious to try" standard to reject claims in unpredictable arts, such as the treatment of cancer. Applicants further direct the Examiner's attention to MPEP 2143 (E) which sets forth the Examiner's burden, according to the USPTO, to properly rejection claims based on an "obvious to try" standard.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants arguments, the Examiner recognizes that Applicants appear to be of the position that the Examiner has applied the "obvious to try" standard. However, the Examiner recognizes that this is not the case. As set forth above, one would have been motivated to combine the teachings of the references because each have been individually taught in the prior art to be affecting at treating cancer. Hence, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, one of ordinary skill in the art would have

reasonably expected to treat cancer since both had been demonstrated in the prior art to be effective. As such, the Examiner has applied the TSM, e.g., teaching, suggestion or motivation, rationale, and not the "obvious to try" rationale as asserted by Applicants.

Claims 32, 41 and 44-45 remain rejected under 35 U.S.C. 103(a) as being unpatentable over O'Reilly et al. (WO 99/43320 A1, 1999, of record) in view of Nakajima et al. (Experimental Cell Research 1998; 241: 126-133).

O'Reilly et al .teach a combination comprising an epothilone and one or more chemotherapeutic agents in the presence or absence of one or more pharmaceutically acceptable carrier materials, as a preparation for simultaneous or chronologically staggered administration to a warm-blooded animal (page 9, last paragraph to page 10, 2nd paragraph). With regards to the epothilone, the WO document teaches that the epothilones include, but are not limited to, epothilone B (page 9, last paragraph). With regards chemotherapeutics, the WO document teaches that the chemotherapeutics include, but are not limited to, 5-fluoruoracil, an anti-androgen or mitoxantrone, an antiestrogen like letrozole, e.g., an aromatase inhibitor, and the taxane class of microtubule stabilizing agents (page 12, last paragraph). In particular, the WO document teaches that chemotherapeutics include, but are not limited to, doxorubicin, e.g., a topoisomerase II inhibitor (page 17, First paragraph). Moreover, the WO document teaches that the combination can be in the form of a kit (page 18, 1st full and 2nd paragraphs).

O'Reilly et al. do not explicitly teach that the second drug is a histone deacetylase inhibitor.

Nakajima et al. teach that a compound referred to as FR901228 is a histone deacetylase inhibitor which is remarkably active in vivo against experimental tumors and is currently under clinical investigation (abstract and page 132, 1st column, last paragraph). Moreover, Nakajima et al. teach that FR901228 exerts its effects by blocking cell cycle transition at G1 and G2/M phases (page 129, 1st column, 1st full paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the epothilone derivative as taught by O'Reilly et al. with a histone deacetylase inhibitor as taught by Nakajima et al. One would have been motivated to do so because each have been individually taught in the prior art to be affecting at treating cancer. Hence, the

instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, one of ordinary skill in the art would have reasonably expected to treat cancer since both had been demonstrated in the prior art to be effective.

In response to this rejection, Applicants request that the Examiner reconsider this rejection in view of the discussion of the rejection over Vite et al. above. Moreover, Applicants assert that the Examiner cites Kerkhoven for the proposition that it is prima facia obvious to combine two composition each of which is taught in the prior art for the same purpose in order to make a third composition for the same purpose. However, Applicants assert that the situation decided in Kerkhoven yielded a predictable result which is clearly distinguishable from the present situation because of the unpredictability in treating cancer. At best, Applicants contend that the combined disclosure of the references suggest an experiment and provide no basis to select an epothilone and a histone deacetylase inhibitor. Lastly, Applicants assert that previously a copy of Funio et al. Mol. Cancer Ther., 2003;2: 971-984, was provided which demonstrates that LAQ824, a histone deacetylase inhibitor, enhances apoptosis of breast cancer cells induced by epothilone B. As such, Applicants assert that this demonstrates an unexpected benefit for the present combination and further, that the LAQ824 is representative of the histone deacetylase inhibitor class and provides an adequate basis to conclude that the entire class would show similar effects. Therefore, Applicants assert that in contrast to the Examiner's previous statement, the data is commensurate with the scope of the claims.

These arguments have been carefully considered, but are not found persuasive.
With regards to Applicants arguments pertaining to Kerkohoven, the Examiner acknowledges and does not dispute Applicants contention that Kerkohoven was related detergents for spay drying, whereas the instant application is directed to methods of treating cancer. However, the Examiner recognizes, for the reasons set forth above, that the fact patterns involved in the present case are analogous to those in Kerkhoven. Briefly, one would have been motivated to combine the teachings of the references because each have been individually taught in the prior art to be affecting at

treating cancer. One of ordinary skill in the art would have reasonably expected to treat cancer since both had been demonstrated in the prior art to be effective. Regarding, Applicants contention that the treatment of cancer is unpredictable, the Examiner acknowledges and does not dispute Applicants contention that the treatment of cancer in general is unpredictable. However, the Examiner recognizes that each of the compounds have been individually taught in the prior art to be effective at treating cancer. As such, there is a reasonable expectation that a combination of the two agents would be effective at treating cancer. Moreover, Applicants have not set forth any evidence that the combination of two agents known to be effective at treating cancer individually, would not be effective at treating the same cancer. Lastly, with regards to the reference provided and Applicants contention of unexpected results, the Examiner acknowledges and has carefully reviewed this reference. However, it is still unclear how this demonstrates patentability of the present claims. Applicants are reminded that the evidence relied *>upon< should establish "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance." Ex parte Gelles, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992) (Mere conclusions in appellants' brief that the claimed polymer had an unexpectedly increased impact strength "are not entitled to the weight of conclusions accompanying the evidence, either in the specification or in a declaration."). In the present case, Applicants assert that an enhancement of apoptosis of breast cancer cells induced by epothilone B by LAQ824 demonstrates an unexpected benefit. However, it is unclear what is to be expected. Applicants are remind that evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) and MPEP § 716.02(d) - § 716.02(e). See In re Blondel, 499 F.2d 1311, 1317, 182 USPQ 294, 298 (CCPA 1974) and In re Fouche, 439 F.2d 1237, 1241-42, 169 USPQ 429, 433 (CCPA 1971). Moreover, Applicants arguments pertaining to the class of deacetylase inhibitors appear to contradict the definition of unexpected, since Applicants infer that the results seen with LAQ824 are predictive of the class of histone deacetylase inhibitors. Thus, it is unclear how something could be unpredictable, but predictable. Accordingly, the rejection is maintained.

Therefore, No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf
Primary Examiner
Art Unit 1642

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Primary Examiner, Art Unit 1642